b. a second element comprising a translocation element derived from a Clostridial neurotoxin able to facilitate the transfer of a polypeptide across a vesicular membrane in a pancreatic cell, and

F1 c. a third element, linked to and comprised in a separate polypeptide chain from said first and second elements, comprising a therapeutic element derived from a Clostridial neurotoxin able, when present in the cytoplasm of a pancreatic cell, to inhibit or block enzymatic secretion by said pancreatic cell,

wherein following binding of said first element said composition is transported across a pancreatic cell membrane.

REMARKS

Applicants thank the Examiner for indicating that the election of species requirement between SEQ ID NO: 2-6 has been withdrawn, and for indicating that claims 1-24 are currently under examination.

Applicants understand that the Examiner has maintained the election of species requirement concerning a composition having a specific translocation element, therapeutic elementy and spacer moiety, and is currently examining the invention provisionally elected by the Applicants in Paper No. 6.

Rejection of Claims 1-24 under 35 USC § 112(1)

The Examiner has rejected all of the the pending claims as lacking written description in the specification adequate to inform the person of ordinary skill in the art that the Applicants had possession of the invention as currently claimed as of the filing date. Applicants have amended claim 1 to indicate that the translocation and therapeutic elements are derived from a Clostridial neurotoxin. Applicants respectfully traverse this rejection as it may be held to apply to the amended claims.

Applicants initially note that Claims 2-24 are original claims and currently stand in exactly the form as they did on the priority date of the current application. Claim 1 has been twice amended since such time. The first amendment was made in Paper No. 8, and merely clarified a) that the translocation across a vesicular membrane takes place in a pancreatic cell, and b) that the claimed composition may block enzymatic secretion. These changes were supported by the specification at e.g., page 11, lines 11-22 and page 11, lines 28-29, respectively.

The second amendment of Claim 1 was made in Paper No. 10, in which Applicants added the requirement that the claimed composition be transported across a pancreatic cell membrane. This is, of course, an essence of the present invention and is supported by the specification at e.g., page 11, lines 11-16. Finally, the claim has now been amended to make clear that the therapeutic element is comprised in a different polypeptide chain than said first and second element. The current amendment is supported by the specification at, e.g., page 32, lines 19-24, page 33, lines 5-16, and page 23, lines 11-21. Thus, all amendments of claim 1 have explicit support in the specification.

The Examiner has cited both *Regents of University of California v. Eli Lily & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997) (hereinafter *Lily*) and the *PTO Final Examiner Guidelines on Written Description Requirement,* 66 Fed. Reg. 1099 (January 5, 2001) (hereinafter the *Guidelines*) as supporting the rejection of claims 1-24. Applicants note that the latter citation "does not constitute substantive rulemaking and hence does not have the force and effect of law." *Guidelines* at 1104 (emphasis added). However even if it did, neither of these references support or provide authority for the Examiner's rejection.

Both under *Lily* and controlling precedent decided prior to *Lily* it is well established that the written description requirement requires the Applicant to describe a claimed invention in a manner which indicates to the person of ordinary skill in the art that Applicants "invented the claimed invention" as of the filing date. *Lily*, 43 USPQ2d at 1404. However, contrary to the Examiner's position, *Lily* does not stand for the proposition that each and every embodiment of a claimed invention must be explicitly described.

In *Lily*, the patentee claimed a cDNA consisting essentially of an DNA sequence encoding proinsulin; human proinsulin was specifically claimed in dependent claims. The specification only included the nucleotide sequence of a single rat insulin cDNA. The *Lily* court first found the human proinsulin claims violated the written description requirement, because "[n]o sequence information indicating which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA" in the patent. *Id.* at 1405.

However, the *Lily* court also reiterated the long-standing rule that patent "applicants are not required to disclose every species encompassed by their claims" *Id.* at 1406 (citation omitted). The court stated that the rules governing written description of a genus are "analogous to enablement of a genus . . . by showing the enablement of a representative number of species within the genus." *Id.* Moreover, the Applicant need not describe what is known in the art.

In the present case, Applicants have disclosed and fully described the *Clostridium botulinum* type A neurotoxin molecule, and the translocation and therapeutic portions thereof. The nucleotide/amino acid sequences of all other types of *Clostridium botulinum* neurotoxins are known and available to those using Genbank. Applicants have given 6 specific examples of binding elements. Applicants have provided an example of the optional spacer moiety, and have described many other such spacers. Such disclosure provides an abundance of examples of species comprised in the claimed genus; more than sufficient to provide adequate written description in the specification for the pending claims as required by *Lily*.

The *Guidelines* are fully consistent with this position. As stated by the *Guidelines*, there is a strong presumption that originally filed claims (such as claims 2-24) meet the written description requirement. For claims such as Claim 1, which are drawn to a genus, "[t]he written description requirement may be satisfied through sufficient description of a representative number of species by . . . disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure . . . ." *Guidelines* at 1106. Applicants submit that the examples of preferred embodiments provided in the specification as described above meets the requirement of description of a "representative number of species", and therefore request that the Examiner reconsider and withdraw this rejection.

Rejection of Claims 1-24 pursuant to 35 USC§103(a)

Claims 1-12 were rejected as allegedly obvious over Shone et al, in view of Gaisano et al, Kennedy et al and Ganog et al. Claims 13-24 were rejected over these references in view of Foster et al and Dangl et al. Applicants respectfully traverse this rejection for the following reasons.

Shone discusses recombinant polypeptides based upon *Clostridium botulinum* neurotoxins, in which the translocation element and endopeptidase of the wild type neurotoxin are retained, but the targeting function of the neurotoxin Hc domain is removed. The purpose of such polypeptides is "to overcome . . . problems associated with production of handling of clostridial toxin", Shone at 3, by removal of the binding region of the native neurotoxin. Significantly, the described polypeptide is "a single polypeptide", Shone at page 4, bottom of page, and is "not composed of two or more polypeptides" Shone at 6, bottom of page.

The Examiner has stated that Shone discloses that "activity of the clostridial neurotoxins [in inhibiting exocytosis] has been observed almost universally in eukaryotic cells expressing a relevant cell surface receptor." However, the referenced "relevant cell surface receptor" is, of course, the same (or substantially similar) to the native receptor displayed by motor neurons normally affected by botulism toxicity – the identity of this receptor is "currently not understood, and no specific receptor species have yet been identified." Shone at 3. Therefore the cells referenced by Shone are either neural cells or cells otherwise displaying the relevant neural cell receptor. Shone provides no hint as to the characteristics of receptors required not just for specific binding, but for endocytotic uptake of the toxin.

The Examiner also characterizes Shone as suggesting that cells affected by clostridial neurotoxins may be neuronal or non-neuronal. However, Applicant respectfully disagrees. The quoted passage concerns only the "first domain" (neurotoxin light chain endopeptidase) of clostridial neurotoxins. Shone states that this endopeptidase, when introduced within some neuronal or non-neuronal cells, will cleave one or more vesicle or plasma-membrane associated protein. Shone at 4, last full paragraph.

The Examiner is correct in stating that Shone discloses that his polypeptide may be adapted to comprise a third domain adapted for binding to desired cells. However, it is unclear from reading Shone how this would work. Specifically (and contradictorily), Shone

indicates that "polypeptides of the invention . . . are not active or their activity is significantly reduced . . . ." Shone at 6, last sentence. Such polypeptides may then be extrinsically activated by treatment with trypsin, *Id.* at 7, but Shone does not indicate how this would occur in vivo. Nor does Shone indicate that mere binding to a cell's surface is sufficient to stimulate endocytosis of the polypeptide.

It is also clear that in this embodiment Shone is still considering that non-native target cells will be neural cells, since the only examples of such non-native target cells given are cells "in which secretion of neurotransmitter is inappropriate or undesirable or alternatively where a neuronal cell is hyperactive." Shone at 11, first full paragraph.

Thus, Shone provides no disclosure which would suggest the presently claimed compositions (e.g., claim 1), which contain a translocation element, a pancreatic cell binding element, and a therapeutic element on another polypeptide chain, much less any disclosure that gives a reasonable expectation that such a composition would in fact function to treat acute pancreatitis.

The addition of the other references cited by the Examiner does not cure this deficiency. Gaisano has been addressed by the Applicants in the past; the reference provides no disclosure beyond the mere showing that permeabilized pancreatic acinar cells given a clostridial neurotoxin light chain can under certain conditions cleave some SNARE proteins and decrease zymogen granule exocytosis. Applicants hereby incorporate the arguments made in previous Replies with regard to Gaisano.

Kennedy and Ganong discuss the binding of CCK-A to CCK receptors on pancreatic acinar cells, and the various forms of CCK, respectively. The references do not suggest that a therapeutic polypeptide containing a CCK binding moiety (or any other acinar cell receptor binding moeity) would be internalized and processed to liberate a therapeutic element within the cytoplasm, nor does their combination with Shone or Gaisano so suggest.

Foster has been discussed at length in previous replies, and these arguments bare incorporated by reference herein. While Dangl may discuss the immunoglobulin hinge region of immunoglobulin molecules, it does not suggest the claimed recombinant composition containing such a hinge region, or methods of treating acute pancreatitis, either alone or in combination with the cited references.

As has been stated in previous Replies, Applicants respectfully maintain that the Examiner has inadvertantly engaged in improper hindsight reconstruction of the claimed invention by first hunting for various elements of the invention in the literature, and then

using the present specification to find the motivation for their combination. As has been stated by the Court of Appeals for the Federal Circuit, "that all elements of an invention may have been old (the normal situation), or sole old and some new, or all new, is however, simply irrelevent. Virtually all inventions are combinations and virtually all are combinations of old elements." *Rosemount, Inc. v. Beckman Instruments, Inc.*, 221 USPQ 1 (Fed. Cir. 1984). The United States Supreme Court, in promulgating the obviousness inquiry in use for 35 years, stated that it is always necessary to "guard against slipping into use of hindsight . . . [and] resist the tempation to read into the prior art the teachings of the invention in issue. *Graham v. John Deere Co.*, 383 U.S. 1, 35-36 (1996) (citations omitted). Applicants submit that this is exactly what has occurred in this situation, and respectfully request the Examiner to reconsider and withdrawn the current rejections.

CONCLUSION

For the reasons given above, Applicants again respectfully urge the Examiner to reconsider rejection of the pending claims. If any fee is required in connection with this communication; please use Deposit Account 01-0885 for payment of any fee that may be due.

Respectfully submitted,

Date: 7/27/01

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MARKED-UP COPY OF AMENDED CLAIM

2. (Thrice Amended) A composition for the treatment of acute pancreatitis in a mammal comprising,

d. a first element comprising a binding element able to specifically bind a pancreatic cell surface marker under physiological conditions,

e. a second element comprising a translocation element derived from a Clostridial neurotoxin able to facilitate the transfer of a polypeptide across a vesicular membrane in a pancreatic cell, and

f. a third element, linked to and comprised in a separate polypeptide chain from said first and second elements, comprising a therapeutic element derived from a Clostridial neurotoxin able, when present in the cytoplasm of a pancreatic cell, to inhibit or block enzymatic secretion by said pancreatic cell,

wherein following binding of said first element said composition is transported across a pancreatic cell membrane.